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A CONTRIBUTION TO THE KNOWLEDGE OF THE ACTION OF CACODYLIC ACID ON THE ANIMAL ECONOMY.

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The only arsenic compounds in which the toxic properties of the arsenic is doubtful are the so-called arsenic-methyl bodies or cacodyl compounds. In the literature of the subject much conflicting testimony exists relative to the poisonous properties of these compounds, and especially concerning one of them, cacodylic acid, which has been selected as the subject of investigation in this paper. Cacodylic acid, $(\text{CH}_3)_2\text{AsOOH}$, contains 54.35 per cent. of metallic arsenic equal to 71.4 per cent. of arsenious oxide.

According¹ to Bunsen,¹ who in 1843 was one of the first to investigate the action of this substance upon the animal economy, it has been taken in large doses, and is not in the slightest degree poisonous. Prof. Kürschner² (quoted by Bunsen) in his researches proved the fact without doubt, and Bunsen's earlier observations upon frogs were fully confirmed. Bunsen³ injected six grains of cacodylic acid, presumably by means of a syringe with a long tube attached, into the stomach of a rabbit without the evidence of even the slightest distress on the part of the animal. Seven grains of the acid were injected into the jugular vein of a rabbit without injurious effect. Four grains of the acid were, in a manner not described, injected into the lungs of a rabbit and no symptoms of poisoning were developed. Bunsen concluded from these results that, on account of the manner of combination of the arsenic in cacodylic acid, it is deprived of its poisonous properties.

Bunsen⁴ injected eight grams (evidently should be grains) of the acid dissolved in water into the jugular vein of a rabbit without producing any unfavorable symptoms.

Schmidt and Chomse⁵ made three experiments upon animals with *perfectly pure cacodylic acid*, and found it to possess no poisonous properties. Their first experiment was performed upon

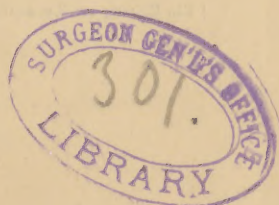
¹ Annalen der Chemie **46**, 10.

² Pogg. Ann. **42**, 140.

³ *Ibid.*

⁴ Annales de Chimie et Phys., 3 Serie, **8**, 358.

⁵ Moleschott's Unters. z. Naturlehre **6**, 122; 1860.



a young cat which had not been fed for twenty-four hours. One gram of cacodylic acid was administered in bread-pills. In thirty minutes the animal showed signs of distress and began to vomit, in which vomit nearly all the pills given were ejected. Very little of the pills was dissolved, as the outside only was softened. Fifteen minutes afterwards the vomiting again commenced, and occurred three times in the following forty-five minutes. During the whole time the cat seemed to be quite lively, and only towards the last, on account of the oft-repeated vomiting, did she show signs of distress.

2. One gram of cacodylic acid dissolved in water was introduced into the stomach of a young cat which had been well fed for twelve hours previously. One and three-quarter hours afterwards vomiting began, which continued for fifteen minutes. Soon afterward liquid feces were ejected, and occurred again two and a quarter hours later. During the whole period the cat showed no other symptoms of distress. She afterward ate with great relish.

3. A mare of torpid constitution, but otherwise physiologically normal (pulse 36, respiration 9), was treated with one gram of cacodylic acid in solution thrown into the left jugular vein. Soon after the injection there was an increase in the pulse, which in the fourth hour settled down to 32. Five hours after the injection nothing other than the previous normal condition of the animal was observed, save that the pulse was 32. In every case cacodylic acid was found by them, in the feces and urine, by reducing the acid to cacodylic oxide with phosphorous acid. Schmidt and Chomse concluded from the result of these experiments that cacodylic acid possessed no poisonous properties.

Lebahn,¹ however, who performed a series of experiments under the direction of Prof. Schulze, Sr., declares from the results of his experiments that cacodylic acid does possess poisonous properties, and that its toxic symptoms are like those of ordinary arsenical poisoning. He experimented wholly upon rabbits, and found that all those (10) to whom the acid was administered died.

Lebahn's Experiments.

1. After the administration of 0.071 gram of cacodylic acid, in four separate portions, into the jugular vein, also dissolved in milk and injected under the skin, the animal died in sixteen days.

¹ Ein Beitrag zur Kenntniss der Wirkung der Kakodylsäure. Dissert., Rostock, 1868.

2. 0.022 gram of the acid given in three portions: twice in milk and once injected under the skin. The animal died in eight days.

3. 0.083 gram of the acid injected under the skin at one time. The animal died in twenty days.

4. 0.166 gram injected under the skin. Animal died in twenty-five days.

5. 0.25 gram injected under the skin. The animal died in eighteen days.

6. 0.2 gram of arsenious oxide injected into the mouth by means of a syringe in two separate portions. Animal died in sixty hours.

7. 0.5 gram of cacodylic acid injected into the mouth. Animal died in ninety-four hours.

8. 0.5 gram of the acid injected into the mouth. Animal died in twenty-three hours.

9. 0.75 gram of the acid injected into the mouth. Animal died in twenty-nine hours.

10. 2.3 grams of the acid, in three portions, injected into the mouth. Animal died in eight days.

Lebahn also found cacodylic acid, as described by Schmidt and Chomse, in the urine and feces by reducing to cacodylic oxide with phosphorous acid.

A quantity of crystalline acid was obtained from a Philadelphia manufacturer of fine chemicals, and the following experiments were performed with one cat and three rabbits:

1.—Sept. 24, 1885. To a young male cat of about 1500 grams weight was administered, at 1.08 P. M., 0.5 gram of cacodylic acid dissolved in about 5 cc. of water. The following effects were produced:

1.45 P. M. Violent retching.

2.35 P. M. Cat vomited. Very sick.

2.40 P. M. Vomited a curdy white material.

2.44 P. M. Vomited a curdy white material.

2.48 P. M. Copious soft, greenish defecation.

2.50 P. M. Marked salivation appeared.

2.52 P. M. Vomited.

2.57 P. M. Vomited and refused to drink water.

3.00 P. M. Copious urination occurred. Cat very restless and in pain. Moaning.

3.10 P. M. Vomited frothy white material. The garlic-like odor due to cacodyl compounds was strongly apparent upon the breath.

The following day (Sept. 25) 0.3 gram of cacodylic acid was given hypodermically to the same cat. Very profuse salivation was immediately noticed. Neither cacodylic acid nor arsenic could be detected in the saliva. The garlic-like odor was again noticed upon the breath. At this juncture the cat escaped, but was recovered two days afterwards in good health.

2.—Sept. 24, 1885. A female rabbit. Weight, about 2500 grams. At 1.30 P. M. 0.1 gram of the acid was administered hypodermically. The animal became very restless. On the following day, Sept. 25, a copious urination occurred at 11.25 A. M. The urine contained jelly-like masses, which under the microscope were found to be mucus. The animal ate food with seeming relish.

3.00 P. M. Urine drawn with a catheter. The presence of cacodylic acid was distinctly determined in it.

3.30 P. M. 0.5 gram of the acid was injected hypodermically. Garlic-like odor was noticed upon the breath. The administration of the acid was stopped. There were no ill effects, except a very noticeable restlessness. The animal entirely recovered.

3.—Sept. 28, 1885. Female rabbit. Weight, 1800 grams.

3.30 P. M. 0.5 gram of the acid was given by the mouth.

4.00 P. M. Salivation noticed. The animal became very sick. No more acid was administered, and the animal fully recovered.

4.—Sept. 29, 1885. Male rabbit. Weight, 1630 grams.

1.00 P. M. Was given 0.5 gram of the acid in solution by the mouth.

1.30 P. M. Animal very restless. Shaking head violently from side to side.

Sept. 30, 1885. Animal ate food readily.

11.25 A. M. Copious discharge of urine, containing jelly-like masses, which proved to be mucus.

1.00 P. M. 0.5 gram of the acid in solution was given by the mouth. Garlic-like odor was very strong on the breath. The animal died during the night.

Post-mortem. Oct. 1, ten hours after death. Stomach full of partly digested grass. Bladder half full of urine. Large intestine greatly distended with liquid colored yellow by feces. The whole alimentary tract showed evidences of a severe gastro-enteritis. Cacodylic acid could not be detected in the brain, but was found

in the kidneys. Phosphorous acid was employed to detect the presence of the acid.

It was observed at this juncture that the cacodylic acid that was employed was not entirely soluble in water, a slight residue always remaining undissolved. Upon examining this insoluble residue microscopically, it was found to be composed of perfectly formed octahedral crystals, which on further testing proved to be arsenious oxide. The remainder of the acid was treated with alcohol, which dissolved the larger part of it. The undissolved portion consisted of octahedral crystals of arsenious oxide. The alcoholic solution was filtered, and the filtrate allowed to evaporate at a low temperature. The resulting crystals were again treated with alcohol, and an insoluble residue of crystalline arsenious oxide was again observed. This recrystallisation after filtration was repeated several times, and each time an insoluble residue of arsenious oxide remained. The fact of this contamination of the cacodylic acid with arsenious oxide necessarily vitiates the results obtained in the preceding experiments.

As Lebahn,¹ in his paper, does not refer to the purity of the cacodylic acid employed by him, it may be possible that the acid he used was contaminated with arsenious oxide, and that the death of the animals used in his observations was not produced by cacodylic acid, but by arsenious oxide.

A new series of experiments was now begun with cacodylic acid obtained from Kahlbaum, of Berlin. It was first, however, thoroughly examined concerning its purity.

1. The crystals were colorless and odorless. Easily soluble in alcohol.

2. An aqueous solution reddened blue litmus.

3. Hydrogen sulphide produced in a water solution a white milkiness, which did not disappear upon boiling.

4. Warmed with phosphorous acid a strong odor of cacodyl was produced, and at the same time the evolution of thick, white fumes of cacodyl oxide was observed.

5. The acid in water solution with mercuric chloride gave a white crystalline precipitate of needle-like crystals, which on heating to boiling did not disappear.

6. A water solution of the acid boiled with red mercuric oxide

¹ *Loc. cit.*

caused no change—*i. e.*, no reduction of mercuric oxide. The filtrate upon cooling was clear, and was not tinged by hydrogen sulphide.

7. The solution of the acid with stannous chloride produced a strong, white cloudiness, and upon warming, a very penetrating odor of cacodyl chloride.

8. Silver nitrate added to a water solution of the acid produced a white precipitate, which on heating turned brown. The liquid had no odor. The precipitate increased upon the addition of ammonium hydroxide, but dissolved in excess of the latter reagent with the production of a brown coloration. Upon boiling this ammoniacal solution a silver mirror was formed, and the liquid became clear and colorless.

9. A water solution of the acid, placed with hydrochloric acid and zinc in a gas-evolution apparatus whose exit-tube led into a solution of silver nitrate, produced a brown, flocculent precipitate in the latter solution, and at the same time, heavy, white fumes were produced in the flask.

10. Barium and calcium hydroxides, calcium chloride and plumbic acetate produced no change in a water solution of the acid.

11. Zinc and platinum in galvanic circuit quickly produced the odor of cacodyl in a water solution of the acid.

It may be taken as conclusive, from the reactions above described, and the physical properties of the crystals employed, that the material was perfectly pure cacodylic acid.

Experiments with Kahlbaum's Cacodylic Acid.

1.—October 10, 1885. A female dog. Weight, 12 kilos.

At 10.35 A. M. 0.5 gram of the acid dissolved in 5 cc. of water was given by the mouth.

10.47 A. M. Vomited. Greatly distressed.

11.05 A. M. 0.5 gram dissolved in 5 cc. of water was given by the mouth. Dog very uneasy. Moaned with pain.

11.27 A. M. Defecated with great pain. Large, dark, loose feces.

12.25 A. M. Vomited curdy white material.

1.15 P. M. 0.1 gram of acid dissolved in 5 cc. of water was given by the mouth. The dog escaped at this juncture, but was recovered three days later in a healthy condition.

November 7, 1885. The dog was kept until this time (twenty-eight days), no more cacodylic acid having been administered since

the amount of 0.1 gram given October 10. The animal was killed, and an autopsy made, which showed an evident gastro-enteritis, and also congestion of the liver, lungs and peritoneum.

2.—October 15, 1885. Dog. Weight, 18 kilos. Dog had not been fed for thirty-six hours.

At 10.30 A. M. 0.2 gram of the acid dissolved in 5 cc. of water was given by the mouth.

10.35 A. M. Salivation produced.

10.50 A. M. Vomited green, frothy matter. Breath had garlic-like odor of cacodyl. Dog lively.

11.30 A. M. 0.1 gram dissolved in 5 cc. of water given by mouth. Garlic odor on breath. Dog lively.

12.30 P. M. 0.1 gram administered as above.

1.30 P. M. 0.1 gram administered as above.

2.30 P. M. 0.1 gram administered as above.

3.30 P. M. 0.3 gram administered as above.

4.25 P. M. Dog vomited, and at same time defecated. Feces soft and yellowish, with a strong garlic-like odor. Dog very sick.

4.30 P. M. 0.2 gram administered by mouth. Dog sick.

4.35 P. M. Vomited.

5.30 P. M. 0.1 gram given by mouth. Breath still has garlic-like odor. Dog very sick.

October 16, 1885. Same dog. Fed at 8.30 A. M. Dog lively. Breath still has garlic odor.

11.00 A. M. 0.2 gram dissolved in 5 cc. of water given by mouth.

11.45 A. M. Vomited.

2.00 P. M. 0.1 gram administered by mouth. Garlic odor.

3.00 P. M. 0.1 gram administered by mouth. Garlic odor.

4.00 P. M. 0.1 gram administered by mouth. Garlic odor.

5.00 P. M. 0.1 gram administered by mouth. Garlic odor.

6.00 P. M. 0.1 gram administered by mouth. Garlic odor.

Dog defecated during the night. Feces were bloody and mucous-like, with garlic-like odor.

October 17, 1885. Same dog. Fed at 8.30 A. M. Lively in spirits.

11.30 A. M. 0.1 gram dissolved in 5 cc. of water given by mouth.

11.50 A. M. Salivation appeared.

12.00 M. Pulse 103; respiration 17. Defecated light yellow mucous-like feces with a strong garlic odor.

12.30 P. M. 0.1 gram was given in a small piece of meat.
 1.30 P. M. 0.1 gram was given in a small piece of meat.
 2.30 P. M. 0.1 gram was given in a small piece of meat. Ate
 a large piece of meat. Dog shows no evidence of distress.
 3.30 P. M. 0.1 gram was given in a small piece of meat.
 4.30 P. M. 0.1 gram was given in a small piece of meat.
 5.30 P. M. 0.1 gram was given in a small piece of meat. Defe-
 cated three times during the night. The feces were soft, slimy,
 mucous-like and streaked with blood.

October 18, 1885. Same dog. Dog lively.

11.00 A. M. 0.2 gram administered in a small piece of meat.

11.35 A. M. Vomited.

12.00 M. 0.2 gram administered in small piece of meat.

1.00 P. M. 0.1 gram administered in small piece of meat.

2.00 P. M. 0.1 gram administered in small piece of meat.

October 22, 1885. Same dog. Condition unchanged. At 1.00
 P. M. 3.0 grams of the acid dissolved in 10 cc. of water were
 injected into the jugular vein.

1.10 P. M. Vomited.

1.15 P. M. Vomited green, slimy material, which when tested
 was found to contain cacodylic acid. There were no solids in the
 vomit. Dog had two large liquid defecations.

October 23, 1885. Dog lively. Eyes congested. Long strings
 of mucus depended from eyelids. Conjunctiva greatly inflamed.

October 31, 1885. Same dog. Condition good. At 1.30 P. M.
 2.0 grams of the acid dissolved in 10 cc. of water were injected
 into the jugular vein.

1.35 P. M. Animal distressed.

1.42 P. M. Vomited slimy, greenish matter, which did not con-
 tain cacodylic acid.

1.55 P. M. Vomited slightly. Same material as before. Caco-
 dylic acid was found in this vomit.

2.00 P. M. Animal greatly distressed.

3.00 P. M. 7.0 grams dissolved in 30 cc. of water injected in
 the jugular vein. No untoward effects were noticed, and fifteen
 minutes later the dog was killed by severing the spinal cord.
 Throughout the whole experiment (seven days) the dog's urine
 was examined for cacodylic acid, which was found in every case.
 The feces of October 16, 17 and 18, treated separately with distilled
 water, warmed, filtered, and the filtrate evaporated to dryness at a

low temperature, showed the presence of cacodylic acid by giving off a strong cacodylic odor when warmed with phosphorous acid.

Results of Autopsy.—Intense inflammation of the stomach, intestines and lungs. Peritoneum injected. The mucous membranes covered with a thick pus. Intensely congested. Spleen enlarged. Kidneys congested.

Microscopic Examination of the Organs.

Lungs.—The blood-vessel walls were thickened, and their lumen everywhere filled with blood. The small capillaries and veins everywhere congested. Lung tissue generally inflamed. The alveolar walls were thickened by cell infiltration, and many of the air vesicles showed distinct catarrhal change, some being filled with epithelial cells, others with a lymphoid exudation, and still others were infarcted with blood. The appearance of the organs generally was that caused by an acute catarrhal pneumonia. In some of the more intensely inflamed portions there was observed numerous yellow, needle-like and cone-shaped crystals resembling hippuric acid. *Spleen.*—Appeared pigmented, which was probably due to the coloring matter of the blood, either in the shape of hæmin crystals or of an amorphous precipitate. The blood-vessels were all intensely congested, and the trabeculæ of the smooth, muscular tissue appeared unusually thick; otherwise nothing abnormal was observed. *Liver and Stomach.*—Showed cloudy swelling of the cells, due to inflammation. *Kidneys.*—Showed same cloudy swelling and a slight degeneration of the epithelium. Heart muscle did not show any morphological changes, and the blood generally was unaltered.

3.—November 3, 1885. Dog of about 15 kilos. weight.

1.50 P. M. 2.0 grams of the acid dissolved in 15 cc. of water were injected into the jugular vein.

1.55 P. M. Dog distressed.

1.56 P. M. Vomited green, slimy material.

1.58 P. M. Vomited same matter again.

2.00 P. M. Defecated. Feces loose and yellowish.

2.02 P. M. Vomited green, slimy material. A very small amount of cacodylic acid was found in this vomit.

2.10 P. M. Distress disappearing. Dog did not die. He was kept in view for several weeks afterward.

4.—November 14, 1885. Dog of 10 kilos. weight.

12.00 M. 3.0 grams of acid dissolved in 20 cc. of water were injected into the jugular vein.

12.10 P. M. Profuse salivation. Respirations, 180 per minute. Dog very sick. Lies down and is unable to get up.

12.35 P. M. Respirations much slower. Dog very uneasy.

12.38 P. M. Attempts to stand, but falls.

12.40 P. M. Gets up and drinks. Staggering gait. Weakness of whole right side manifest.

November 15, 1885. 10.00 A. M. Dog vomited twice during the night. Both ejections contained cacodylic acid. Dog lively and ate with evident relish. This dog lived several weeks, and was subsequently used for other purposes.

5.—November 7, 1885. Small dog weighing about 5 kilos.

2.00 P. M. 3.0 grams of the acid dissolved in 20 cc. of water were injected into the jugular veins.

2.04 P. M. Vomited a small quantity of slimy, greenish matter. No cacodylic acid was found in this vomit.

2.10 P. M. Extreme salivation. Great pain.

3.10 P. M. Staggering gait. Dog leans to the right side. Tactile sensibility lost. Pupils dilated evenly. Respirations slow and labored. Dog moans as if in pain.

3.40 P. M. Dog rises with much difficulty and immediately falls.

4.45 P. M. Dog died.

The evident cause of death in this experiment was the enormous amount of the acid in proportion to the weight of the dog, which was introduced directly into the circulation. Immediately after injecting the acid the blood-pressure tracings were taken with the kymographion, showing slowing of pulse and decrease in arterial pressure.

Autopsy.—Peritoneum greatly injected. Intestines congested and mucous membrane covered with pus. Lungs congested. Left auricle full of dark, unclotted blood. Urine evaporated to dryness and tested showed presence of cacodylic acid strongly.

According to Schmidt and Stürzwag,¹ upon the administration of arsenious oxide nervous symptoms occur, due to spinal irritation and paralysis. To the spinal irritation may be ascribed the vomiting and slowing of respiration, and also the partial paralysis or convulsive movements. These same symptoms occurred in the foregoing experiments with cacodylic acid, except the paralysis

¹ Moleschott's *Unters. z. Naturlehr.* 6, 296.

and convulsive movements, which only existed in a slight degree. Schmidt and Stürzwag observed a decided weakness in the hind extremities, so that the animal was unable to stand. The same was observed in the preceding experiments with the acid. Schmidt and Stürzwag also noticed that a peculiar condition of somnolence occurred, in which movements were uncertain. This was also noticed in these experiments with cacodylic acid. The weakness, however, in all cases experimented upon with the acid was unilateral, resembling hemiplegia. In Schmidt and Stürzwag's cases diarrhoea was observed in nearly all the animals. This was noticed in all the experiments in the present investigation.

Lebahn observed that the action of cacodylic acid and arsenious oxide produce nearly analogous symptoms, and that the pathological changes were the same. The foregoing experiments confirm Lebahn's observations as far as the symptoms are concerned (*i. e.*, the analogous symptoms produced by cacodylic acid and arsenious oxide); but, as has been shown by the experiments described in this paper, cacodylic acid is not fatal in its effects. The fatal terminations in Lebahn's cases were probably due to an impure acid which he may have employed, which, as has been shown in the first part of this paper, may very readily happen. Lebahn concluded from his results that a part of the cacodylic acid was, by the action of the blood, decomposed, and that the arsenic set free entered into combination in its inorganic form with an alkali, and in this manner acted upon the organism. A part of the cacodylic acid may be given off by the lungs as paracacodylic oxide (*vide* the garlic-like odor on breaths), and the rest of it is excreted by means of the urine and feces as cacodylic acid. The formation of paracacodylic oxide may be the cause of the vomiting. Schmidt and Chomse¹ found that by the injection of the acid into the blood no perceptible action was produced. In the experiments described in this paper it may be observed that the action of the acid (causing vomiting, purging, etc.) was the same, whether given by the mouth or injected directly into the circulation. Finally, then, judging from the results of the experiments herein described, it may be concluded that cacodylic acid is not a poisonous substance in the general acceptance of the word poison.

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¹*Loc. cit.*

